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A role for lung retention in the sense of retronasal smell

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Abstract

In olfaction, odors typically engage the lungs on the way to the nose to evoke retronasal smell. This is most notable when the lung has a first pass effect during smoking/vaping, but also upon exhaling after sniffing an odor. The lungs act as a sink for odors, which can both reduce the retronasal odor concentration and the odor mixture makeup. Lung retention is a simple measure that quantifies the effectiveness of the sink. Lung retention has been studied in the context of environmental toxicology and is known for many volatile organic compounds. Available data on human lung retention suggests that the lungs may have a large impact on odor perception, and that this may depend heavily on the specifics of active sampling such as sniffing, smoking and vaping. Suggestions are included for transient measures and models of lung retention.

1. Introduction

Retronasal and orthonasal smell

The sense of smell plays a critical role in terrestrial mammals. It guides mating behavior and selection, predator-prey interactions, foraging, food selection and food appreciation (Shepherd 1988). While smelling is an active process involving complex behaviors such as active sniffing, breathing and chewing, the role of active sampling on the neural processing of odors has only recently begun to be elucidated (Youngentob, Mozell et al. 1987, Verhagen, Wesson et al. 2007, Wesson, Verhagen et al. 2009). Moreover, given that the lungs play a major role in driving odor flows by virtue of their pumping action, it seems surprising that the interaction between the lungs and odors has not been placed in the context of the sense of smell to date. Here I aim to highlight the effects of the lungs on odors in the context of the active sense of smell. \

Two modes of smell exist: orthonasal and retronasal smell. These modes are differentiated by the origin of the odor: orthonasal draws in odors externally by an inward airflow, while retronasal makes odors available internally via an outward airflow (Rozin 1982). Of these two modes, retronasal smell is the most relevant when considering the role of the lungs in olfaction, and therefore it will form the focus for this paper.

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Retronasal smell is ubiquitous, if indirect

Retronasal smell is most strongly evoked by exhalation of odors during eating and is particularly involved in the perception of orally derived food odors entering the nasal cavity via the nasopharynx. Oral odorants, upon chewing or swallowing and exhalation, pass the nasal cavity and exit the nares (Taylor 1996, Hodgson, Linforth et al. 2003).

Aside from orally-derived odors that pass over the olfactory mucosa after leaving the mouth, all other odor trajectories also engage retronasal smell, but only after engaging the lungs. One prominent example occurs during smoking, when smoke is inhaled, engages the lungs and is subsequently exhaled through the nose. Such an effect may be even more prominent when smoking using electronic cigarettes. E-juice, the vaping consumable, is available with a large variety of flavors, which can provide a pleasant aroma when exhaling the aerosol. Lung-derived retronasal smell may also occur during breathing with an open mouth when some of the exhaled air exits via the nose.

In addition, retronasal smell affords an additional chance to sample odor streams that have already been sampled via orthonasal smell. On “first pass” (i.e. orthonasal smell), not all odorant molecules are deposited along on the olfactory mucosa. Some odor-containing air is inhaled, passes through the nasal cavity, enters the lungs and subsequently engages olfactory receptors retronasally during expiration.

2. Lung Retention (LR)

Lung retention: introduction

In the latter two cases, only some odorant particles return to the nasal cavity after inhaled odors are retronasally exhaled. The fraction of particles that do return varies by odor, and can be defined by a measure known as the lung retention (LR) (Jakubowski and Czerczak 2009). Thus, the returned odor mixture is of some lower concentration and different relative composition as the originally inhaled mixture.

Lung retention has been studied in the field of environmental toxicology, where long-term exposure to volatiles leads to their absorption in the body, which can pose health-risks. LR is established by measuring the inhaled odor concentration (typically in a steady state odor environment) and the exhaled odor concentration (Jakubowski and Czerczak 2009). The fraction of the inhaled concentration not exhaled is the percentage lung retention. In the context of smell, we are mostly interested in the inverse: “lung pass”, being the exhaled fraction (100-LR), which subsequently enters the nose retronasally.

Lung retention and smell

To explore the potential of LR to impact smell, data on human LR was used from the toxicological review by Czerczak et al. (Tables 1 and 2, (Jakubowski and Czerczak 2009)). The average LR was calculated for a volatile organic compound (VOC) if multiple studies were reported. Lung pass (LP) was subsequently calculated (100%-LR) and tabulated in Table 1. What is clear from these data is that LR may have a large impact, as only 42±15% of these volatiles is returned from the lungs (LP). It should be noted that these data were obtained after >2hr VOC exposure. Odors with low blood:air partition coefficients (K_b,

~0.3) are known to decrease their LR over the course of such long-term exposure as blood concentrations reach equilibrium between absorption and metabolism/excretion of the VOC. For high K_b values (~4) this appears not to happen and LR is independent of exposure time (Jakubowski and Czerzak 2009). Thus, for the purpose of brief exposure in the context of smell, the lung pass values in Table 1 err on the high side, esp. for odors with a high K_b .

Due to the potentially large effect of lung retention on odors and for clarity of the discussion I suggest a refinement in classifying the process of retronasal smell, depending on the trajectory of the odor, depicted schematically in Figure 1: mouth-lung-nose (MLN), nose-lung-nose (NLN) and mouth-nose (MN). Note that while all trajectories ultimately engage the nasal cavity retronasally, only one route (NLN) effectively engages orthonasally. Also note that the retronasal route is only engaged directly via route C, thus for MLN and NLN, odors engage the lungs.

I will assume that only an insignificantly small fraction of the exhaled oral food odors is subsequently re-inhaled, due to free external odor diffusion and differences between inhaled and exhaled odor flows. Hence, oral food odors (MN, Fig. 1) do not significantly engage the lungs, except perhaps when chewing occurs during inhalation (data on this appears to be lacking).

Lung retention: impact

Table 1, which shows monomolecular LP, provides information in addition to the important notion that common volatiles are readily retained by the lungs. It should be noted up front that the generalizability of these 38 odors to the vast odor space (230 key odors for food and beverages alone (Dunkel, Steinhaus et al. 2014)) is unclear. However, it surely indicates that these organic volatiles display strong lung retention of on average 58%, suggesting that air that enters the nasal cavity via the NLN trajectory has 58% lower odorant concentration compared to the initial condition during orthonasal passage.

Also notable is that the LP varies considerably (10%–77%), and appears to follow a skewed normal distribution. The SD is only an absolute 15%, the coefficient of variation (SD/mean) being 0.35. It thus seems to be a relatively common property of VOCs and reinforces the notion that LR usually plays a significant role in smell. Figure 2 shows the distribution of the number of volatiles from Table 1 and their lung pass fractions, reaffirming that VOCs commonly have a high degree of LR.

Besides reducing the concentration of odors available to retronasal transduction, LR also provides a means to change the composition of odor mixtures, because LR differs for different volatiles. The implication is that, in the NLN pathway, retronasal aroma may not only be less intense, but also qualitatively different from the orthonasal aroma. In order to address this I performed a randomization test (in Matlab) to see if LR affected the odor mixture profile. I randomly selected up to 38 odors from Table 1 and randomly imposed a concentration profile for pre-lung exposure, which was then adjusted to a post-lung profile by LR. The correlation was calculated across the pre- and post-lung mixture profile. This was repeated 100 times per number of odors selected. The pre- versus post-lung odor pattern correlation was very consistent at $r=0.82\pm0.01$ (mean $\pm$ sd across number of odors tested,

$r^2=0.67$), hence independent of the number of odors. This suggests that LR can moderately affect mixture composition (a correlation of 1 meaning no change in composition), by imposing ~33% variation across the profile. For comparison, it has been established that in the rat dorsal OB (no human OB data is available) the correlation of response patterns between ortho- and retronasal monomolecular odor stimulation (bypassing any lung effects) was 0.38 ± 0.09 (mean $\pm$ sem, $r^2=0.14$) (Gautam and Verhagen 2012). To summarize, LR results in roughly half the concentration of odors being available retronasally and a moderate change in odor mixture, compared to when they are sniffed (NLN) or inhaled (MLN).

Lung retention: theoretical estimations

Clearly, the 38 volatiles in Table 1 are insufficient in number to describe the effects of LR for many olfactory-relevant contexts. Two approaches can be taken to estimate the LR when experimental data is lacking. The simplest method is to estimate LR based on physico-chemical properties. The second involves approximating epithelial absorption parametrically.

Czerzak found correlations of 0.82 and 0.73 between the log Kb (blood:air partition coefficient) and long-term exposure LR across odors in Table 1 when VOCs were divided between those with low (<10 g/l) and high (>10 g/l) water solubility, respectively (Jakubowski and Czerzak 2009).

For low water soluble VOCs the prediction is (with a relative 18% SD)

$$LR=27+21 * \log Kb$$

For high water soluble VOCs it is (with a relative SD of 17%)

$$LR=37+10 * \log Kb$$

The Kb can be readily calculated from existing databases of descriptors of over 5000 compounds (see (Jakubowski and Czerzak 2009)). While this is undoubtedly useful for long term LR estimation, relevant e.g. to repeated behaviors like MLN smoking and vaping, it may not be appropriate for transient NLN LR estimates which are not dominated by air:blood partitioning, but by epithelial absorption.

To estimate transient LR the second method (below) may be more useful, though it has yet to be tested experimentally. Before VOCs are absorbed by pulmonary blood, they first have to diffuse through the epithelial alveolar membrane. Due to the transient nature of the exposure, subsequent absorption in the blood may play only a minor role. The simplest estimation of transient LR is based on Fick's Law:

$$V_{\text{gas}} \approx (A * D * P)/T, \text{ where}$$

V_{gas} = the volume of gas diffusing through the epithelium per time (ml/s)

A = the epithelial surface area engaging with the odor (up to 80 m² in adult males)

D = diffusivity of the odor, $D \approx$ solubility in water/ M_w (M_w = molecular weight)

P = the partial pressure of the odor, assuming no odor is present in the lung tissue or blood

T = thickness of the epithelial barrier, $\sim 0.3 \times 10^{-6}$ m

Abraham and colleagues have estimated the air to lung partition coefficients for a large number of VOCs (Abraham, Ibrahim et al. 2008), which could also be of use in modeling transient LR. For further theoretical discussion, see Dubois and Rogers (Dubois and Rogers 1968). This equation suggests that transient LR is increased by deeper inhalation of longer duration of odors with high water solubility and low molecular weight. This is discussed next.

Lung retention depends on specifics of odor sampling

LR during a particular sniff or inhalation cycle will depend on the depth of inhalation, which determines the surface area of the lung that the odor is exposed to. LR is measured under resting conditions with an approximate typical tidal volume of ~ 0.5 L. LR is also likely to depend on the time the odor resides near the lung interface to allow absorption. Further, during inhalation the odor is also diluted in the lungs, which can be assumed to have a typical residual volume of about 1 liter. Active orthonasal odor sampling is task-, odor- and concentration-dependent and varies between subjects (Laing 1982). Laing reported huge differences between subjects in sniffing behavior in detecting odors or rating their intensity (Laing 1982). For example, total inspired volumes ranged approximately 10-fold (c.f. Table 3), e.g. 143–2174 ml for 1.2ppm pentyl acetate during a detection task. This parameter alone is likely to yield large variance in the impact of LR (and dilution) on NLN retronasal smell in practice. However, experimental data on how LR depends on active NLN sampling appears lacking.

MLN sampling varies as well. Smoking behavior has been reviewed in Marian et al. (Marian, O'Connor et al. 2009) and Kleinstreuer et al. (Kleinstreuer and Feng 2013) and typically follows the cycle of puffing, mouth holding, inhalation, exhalation and an inter-puff interval, but the exact detailed order of behavior (not described here) can vary. It is known that there exists large inter-individual variation in smoking behavior (Marian, O'Connor et al. 2009, Kleinstreuer and Feng 2013). In smoking the puffing and inhalation patterns have been shown to vary with nicotine content of the cigarette in most studies (Scherer 1999). Puff volumes are increased as the nicotine yield of the cigarette decreases, but inhalation depth does not appear to change (Scherer 1999). Robinson et al. (Robinson, Pritchard et al. 1992) report 52 ± 5 ml (mean $\pm$ se) puff volumes, 845 ± 105 ml inspiratory volumes and 891 ± 101 ml expiratory volumes for regular male adult smokers smoking a regular cigarette. This compares to a 45 ± 11 ml (mean $\pm$ sd) puff volume, 636 ± 138 ml inhaled volume and 655 ± 195 ml exhaled volume in the BAT study reviewed in Marian (Marian, O'Connor et al. 2009). Puff volume increases and inter-puff interval decreases during the smoking of a cigarette (Marian, O'Connor et al. 2009). In their review, Marian (Marian, O'Connor et al. 2009) reports that nicotine retention is independent of inhalation volume, due to its very rapid absorption in the lungs. On the other hand, nitrosamines and solanesol were more retained with increased inhalation volumes. This suggests that LR is indeed

affected by active sampling in the MLN pathway. The sense of smell also plays a role in this sampling: nose clips modify smoking behavior, especially reducing perceived “taste” (flavor), satisfaction and puff volumes (Baldinger, Hasenfratz et al. 1995), showing that MLN-mediated smell (or at least retronasal airflow) is critically involved in this process. Personal observations of smokers suggest that the aerosol of flavored electronic cigarettes is frequently exhaled via the nose, suggesting an even larger role of the MLN pathway in vaping. Vaping has been widely adopted by both adolescents and adults (7% and 10%, respectively, in 2012 (Chapman and Wu 2014)).

Integration: monomolecular concentration

It will be useful to be able to approximate the relative strength of the degree to which odors are able to activate the olfactory epithelium (OE), as a starting point to approximate the relative perceptual impact. To estimate the perceptual impact relative to direct orthonasal smell I suggest the following simplified convolutions (referring to Fig. 1), each reducing the engagement of an odor during its ultimate retronasal epithelial passage:

$$\begin{aligned} \text{MLN}_i &: \text{MR}_i * \text{LR}_i * \text{RE}_i \\ \text{NLN}_i &: \text{NR}_i * \text{LR}_i * \text{RE}_i \\ \text{MN}_i &: \text{MR}_i * \text{RE}_i \end{aligned}$$

where MR=mouth-throat retention, LR=lung retention, NR=nose retention, RE=retronasal OE engagement efficiency relative to orthonasal route, i=a monomolecular odor.

RE can be established using theoretical models, but has also experimentally been established in anesthetized rats in the dorsal OB (Gautam and Verhagen 2012) (bypassing the lungs; human data is not available), yielding an average of $63 \pm 12\%$ efficacy of retronasal compared to orthonasal stimuli (see also (Scott, Acevedo et al. 2007, Furudono, Cruz et al. 2013)). Thus, in rat OB retronasal response amplitudes tend to be 63% of orthonasal responses to the same odors. Note that both rats and mice can detect odors retronasally (Gautam and Verhagen 2012, Rebello, Kandukuru et al. 2015). Also note that these OB-based data pertain to ORN neural activity levels and not directly to odor concentration, thereby indicating an initial estimate of perceptual odor intensity. How closely rodent RE reflects human RE cannot yet be established, and must hence be taken as tentative.

Nose and mouth retention are likely to be comparatively small, due to their relatively small surface area compared to the lungs ($\sim 80\text{m}^2$ for the lungs). In this case, the above convolutions can be simplified further to:

$$\begin{aligned} \text{MLN}_i &= \text{NLN}_i : \text{LR}_i * \text{RE}_i \\ \text{MN}_i &: \text{RE}_i \end{aligned}$$

Based on the above-mentioned average values these equations roughly yield for an average odor:

$$\text{MLN} = \text{NLN} \cdot 0.42 \cdot 0.63 = 0.26$$
$$\text{MN} : 0.63$$

In conclusion, at first approximation the combination of lung retention and nasal route may typically result in a large ~74% reduction in odor intensity retronasally compared to what is inhaled or sniffed. Both LR and odor route across the nasal epithelium have comparably large effects.

This approach ignores the dynamics of odors, i.e. the odor time-concentration profiles. Time can be included, if known. It has been suggested that the OE can act as a chromatograph - a chemical spatio-temporal “delay line” (Mozell 1970, Mozell, Kent et al. 1991). Given the histological similarity between nasal and pulmonary epithelium, it seems likely that the lungs too can impose such temporal order on odor dynamics as a function of odor properties. This has yet to be described, but could be important.

3. Implications and limitations

Here I highlighted the potential for the lungs to impact the sense of smell. A readily available measure, LR, provides a first insight into this role. The lungs not only drive breathing and sniffing, but also act as a sink for odors. This will likely reduce the impact of retronasal odors after either orthonasal sniffing or oral inhalation. It may also affect the mixture composition of odors.

However, we don't know the LR for many odors as LR has been established mainly to assess the impact of toxicological environmental exposure to VOCs. I provided two approaches towards estimating LR, but these require further development and validation. Further, known LR values are mostly established after long-term (>1hr) exposure to a steady state odor concentration. This does not mimic conditions during which LR may impact the sense of smell during active sampling of NLN odors. It hence would be useful to establish transient LR for a large array of odors under smell-relevant conditions. These will have to take VOCs naturally present in the breath into account (Dent, Sutedja et al. 2013). Thrall and colleagues have demonstrated the dynamics of human lung and nasal epithelial retention of acetone and toluene using a sophisticated rapid sampling approach (Thrall, Weitz et al. 2002, Thrall, Schwartz et al. 2003). This approach may lead the way toward establishing a database to explore the role of dynamic lung retention on the sense of smell. A simpler short-duration steady-state approach has also been reported for human nose and lung retention of 4 compounds (Landahl and Herrmann 1950). LR for the NLN pathway will also depend on the odor scrubbing ability of the upper respiratory tract, which can be very significant, and has been reviewed by Morris (Morris 2001).

Computational modeling of airflow and odor absorption along the entire the human respiratory system will be crucial to elucidate the mechanisms involved (Kleinstreuer and Zhang 2010, Walters and Luke 2011) and could be used to explore differences in the LR of VOCs in the gas-phase, in a liquid and gas-phase equilibrium in aerosols (vaping), and in solid-phase aerosols (smoke) (Caldwell, Sumner et al. 2012, Burstyn 2014, Oh and Kacker

2014). Of particular relevance is the study by Zhang et al., which showed similar particle size distributions among conventional cigarette and e-cigarette aerosols of 100–600nm and suggest that 9–17% is absorbed in the upper airways and 9–18% in the alveoli (Zhang, Sumner et al. 2013).

One pertinent question is what the perceptual consequences may be of LR. I am not aware of any studies exploring MLN or NLN retronasal smell. How intense is an odor during exhalation after sniffing (inhalation)? How similar is the odor quality between inhalation and subsequent exhalation? Research on retronasal smell appears confined to oral food perception to date. I provided some initial estimates of what the impact might be. However, these estimates excluded many other factors like odor concentration, neural adaptation, the (low) slope of the concentration-intensity function and attention. I nonetheless hypothesize that LR significantly reduces NLN and MLN odor intensity and moderately affects NLN and MLN odor quality.

VOCs absorbed by the lungs could impact the physiology of the olfactory system and could affect body odor if exposure is of sufficient duration and concentration. The author is not aware of studies showing modulation of the olfactory system or effects on body odor by VOCs (unlike endogenous compounds) carried in the blood circulation.

MLN based aroma from smoking and vaping suggests a significant role for LR on electronic cigarette flavor perception. The increasing popularity of vaping and the extensive flavoring used in e-liquids suggest that LR (both transient and long-term) will be important in understanding both the health impact and perceptual impact the lungs may have in this behavior.

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Figure 1.

Three routes of odor transport and relation to lung retention.

MLN: mouth-lung-nose, where odorants enter via the oral cavity. This is most common during smoking or breathing with open mouth. Lung retention occurs.

NLN: nose-lung-nose, where odors enter via the nose. This occurs commonly during orthonasal smell while sniffing or breathing with closed mouth. Lung retention occurs.

MN: mouth-nose, where odors originate in the oral cavity and pass directly to the nose. This is typical of retronasal smell during food intake. Lung retention does not occur.

OE: Olfactory epithelium.

Figure 2.
The distribution of Lung Pass (i.e. 100-LR%) for the 38 volatiles of Table 1.

Table 1

Organic volatiles and the inverse of their lung retention (i.e. “Lung Pass”, %). Left two columns: organized alphabetically. Right two columns organized by LP.

ODOR	100-LR	100-LR	ODOR
1,1,1-Trichloroethane	74	10	Aniline
1,2,3-Trimethylbenzene	29	19	Dimethylformamide
1,2,3,5-Tetramethylbenzene	34	20	Nitrobenzene
1,2,4-Trimethylbenzene	32	22	Furfural
1,2,4,5-Tetramethylbenzene	31	24	EGME
1,3,5-Trimethylbenzene	33	29	1,2,3-Trimethylbenzene
Acetone	51	30	Dichloromethane
Acrylonitrile	48	31	1,2,4,5-Tetramethylbenzene
Aniline	10	32	1,2,4-Trimethylbenzene
Benzene	44	32	Phenol
Carbondisulphide	60	33	1,3,5-Trimethylbenzene
Cyclohexanol	36	34	1,2,3,5-Tetramethylbenzene
Cyclohexanone	42	34	Styrene
Dichloromethane	30	35	Xylenes
Dimethylformamide	19	36	Cyclohexanol
EGGE	36	36	EGGE
EGME	24	39	Tetrachloroethylene
ETBE	67	40	Methylisobutylketone
Ethylbenzene	51	40	Tetrachloroethylene
Ethyleneglycolmonoethyletheracetate	43	42	Cyclohexanone
Ethyleneglycoln-butylether	43	42	Methanol
Furfural	22	43	Ethyleneglycolmonoethyletheracetate
Methanol	42	43	Ethyleneglycoln-butylether
Methylethylketone	47	44	Benzene
Methylisobutylketone	40	47	Methylethylketone
MTBE	56	47	Toluene
n-Butanol	53	48	Acrylonitrile
n-Hexane	77	49	tert-Amylmethylether
Nitrobenzene	20	49	Trichloroethylene
Phenol	32	51	Acetone
Styrene	34	51	Ethylbenzene
tert-Amylmethylether	49	53	n-Butanol
Tetrachloroethylene	39	56	MTBE
Tetrachloroethylene	40	60	Carbondisulphide
Toluene	47	60	Vinylchloride
Trichloroethylene	49	67	ETBE

ODOR	100-LR	100-LR	ODOR
Vinylchloride	60	74	1,1,1-Trichloroethane
Xylenes	35	77	n-Hexane

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